PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BOGENSBERG PATENT- & MARKENBÜRO
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.09.2005
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
B-P-5674-WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/002637	12.03.2004	18.03.2003

Applicant
NOWICKY, Wassyl

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B-P-5674-WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/002637	International filing date *(day/month/year)* 12.03.2004	Priority date *(day/month/year)* 18.03.2003
International Patent Classification (IPC) or national classification and IPC A61K35/78, A61K31/14, C07D221/18, C07D491/22, C07F9/564, C07F9/6561, C07F9/59, C07F9/6533, C07F9/6509, C07F9/6584, C07F9/6539, C07G5/00		
Applicant NOWICKY, Wassyl		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.10.2004	15.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Elliott, A Telephone No. +49 89 2399-8218

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/002637

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1, 3-22	as originally filed
2, 2a	received on 14.06.2005 with letter of 07.06.2005
Claims, Numbers	
1-25	received on 25.10.2004 with letter of 21.10.2004
Drawings, Sheets	
1/11-11/11	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/002637

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-25
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4, 6-17, 21-23 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4, 6-17, 21-23 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. VIII Certain observations on the international application

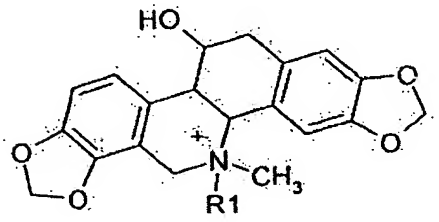
The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

In amended form the application relates to a process for the manufacture of an alkaloid reaction product comprising at least one alkaloid derivative having a quaternary nitrogen. The process comprises alkylating at least one alkaloid present in the herb Chelidonium majus L. in an organic solvent, subjecting the resulting reaction mixture to at least one washing step with an aqueous solvent or water and subjecting the washed reaction mixture to treatment with a strong acid in gaseous or liquid form to convert the derivative into a water-soluble form.

The application is further directed to an alkaloid reaction product comprising at least one alkaloid derivative other than sanguinarine and N-methylprotopine chloride, the derivative having a quaternary nitrogen and the alkaloid being selected from the group of alkaloids present in the herb Chelidonium majus L. for use as a drug or medicament.

Further claimed is a chelidonine derivative according to formula



(I)

wherein R1 is hydrogen, methyl or ethyl, for use as a drug or medicament.

Also claimed is the use of an alkaloid reaction product comprising at least one alkaloid derivative other than sanguinarine and N-methylprotopine chloride, the derivative having a quaternary nitrogen and the alkaloid being selected from the group of alkaloids present in the herb Chelidonium majus L. in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a disease or bodily condition selected from the group consisting of viral infection, cancer, immunological dysfunction, metabolic dysfunction and radiation damage.

Further claimed is the use of the chelidonine derivative of formula (I) above in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a

disease or bodily condition selected from the group consisting of viral infection, cancer, immunological dysfunction, metabolic dysfunction and radiation damage.

Basis is to be found in the original application documents for the subject-matter of the amended claims - Article 34(2)(b) PCT is therefore satisfied.

The prior art documents listed in the search report will be referred to as follows:

D1: DATABASE CHEMICAL ABSTRACTS [Online] Database accession no. 1982:173909 & ZHAO Y ET AL: 'Studies on the antimalarial activity of protopine derivatives' CHINESE PHARMACEUTICAL BULLETIN (YAOXUE TONGBAO), vol. 16, no. 6, June 1981, pages 7-10

D2: TANAKA S ET AL: 'Influence of natural and synthetic compounds on cell surface expression of cell adhesion molecules, ICAM-1 and VCAM-1' PLANTA MEDICA, vol. 67, no. 2, 2001, pages 108-113

D3: SCHMELLER T ET AL: 'Biochemical activities of berberine, palmatine and sanguinarine mediating chemical defence against microorganisms and herbivores' PHYTOCHEMISTRY, vol. 44, no. 2, January 1997, pages 257-266

D4: SCHLOTTERBECK J O ET AL: 'Beiträge zur Chemie des stylophorum diphyllum' CHEMISCHE BERICHTE, vol. 35, 1902, pages 7-23

D5: HENSCHKE A: 'I. Über das Chelidonin' ARCHIV DER PHARMACIE, vol. 226, 1888, pages 624-644

D6: WALTEROVÁ D ET AL: 'Inhibition of liver alanine aminotransferase activity by some benzophenanthridine alkaloids' JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 9, September 1981, pages 1100-1103

D7: ISHII H ET AL: 'Studies on the chemical constituents of rutaceous plants. LX. Development of a versatile method for syntheses of the antitumour benzo[c]phenanthridine alkaloids. 9. Efficient syntheses and antitumour activities of nitidine and related non-phenolic benzo[c]phenanthridine alkaloids' CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 33, no. 10, 1985, pages 4139-4151

D8: LOMBARDINI J B ET AL: 'Effects of benzophenanthridine alkaloids on the phosphorylation of an approx 44 kDa protein present in a mitochondrial fraction of the rat heart' BIOCHEMICAL PHARMACOLOGY, vol. 51, no. 2, 26 January 1996, pages 151-157

D9: NAKANISHI T ET AL: 'Structural considerations of NK109, an antitumour benzo[c]phenanthridine alkaloid' JOURNAL OF NATURAL PRODUCTS, vol. 62, no. 6, June 1999, pages 864-867

D10: VALPUESTA M ET AL: 'From protopines to berbines: synthesis of 1-methoxystylopine and its N-metho salts from coulteropine' TETRAHEDRON, vol. 58, no. 25, 17 June 2002, pages 5053-5059

D11: SLAVIK J ET AL: 'Quaternary alkaloids from the roots of Argemone platyceras LINK et OTTO' COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 41, 1976, pages 285-9

D12: SCHMIDT E: '46. Über Paveraceen-Alkaloïde' ARCHIV DER PHARMACIE, vol. 231, 1893, pages 168-183

D13: TAKAO N ET AL: 'Studien über die Alkaloide de Pavaveraceen. Die Alkaloide von Corydalis incisa. (10). Über die struktur des (+)-14-Epicorynolins' CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 21, 1973, pages 1096-1102

D14: DANCKWORTT P W : 'Zur Kenntnis des Protopins und Kryptopins' ARCHIV DER PHARMACIE, vol. 250, 1912, pages 590-646

D15: MANSKE R H F ET AL: 'The alkaloids of papaveraceous plants. XXXIV. Hunnemannia fumariaefolia Sweet and the constitution of a new alkaloid, hunnemanine' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 64, no. 7, July 1942, pages 1659-1661

D16: REDEMANN C E ET AL: 'Characterisation of certain alkaloids from Fagara coco' JOURNAL OF THE

AMERICAN CHEMICAL SOCIETY, vol. 71, no. 3, 19 March 1949, pages 1030-1034

D17: ULRICHOVÁ J ET AL: 'Cytotoxicity of natural compounds in hepatocyte cell culture models. The case of quaternary benzo[c]phenanthridine alkaloids' TOXICOLOGY LETTERS, vol. 125, no. 1-3, 15 December 2001, pages 125-132,

D18: ZHANG G-L ET AL: 'Alkaloids from Dactylicapnos torulosa' PHYTOCHEMISTRY, vol. 40, no. 1, 1995, pages 299-305

Re Item III.

As already indicated in the search report, the search was limited to the reaction products of the particular alkaloids given in original claim 4 and the chelidonine derivatives of original claim 9. Therefore this opinion is to be only regarded as complete for the subject-matter of the amended claims which relates to these particular alkaloids and the particular chelidinone derivatives.

Re Item IV.

With a number of compounds being already known in the art, unity is not considered present between the methods for preparing the compounds and the use of the compounds for preparing medicaments:

In D1, the compound A2 (protopine methyl iodide).
D10 discloses the compounds 3a, 3b, 4a, 4b, 5a and 5b.
D11 discloses stylopine methiodide and methperchlorate.
Methyliodide homochelidonine is disclosed on page 168 of D12.
Compound 4 from D13.
D14 gives a number of derivatives of protopine (cf. pages 632-9).
Hunnemanine-O-ethyl ether disclosed in column 2 on page 1660 of D15.
Fagarine (otherwise known as allocryptopine) derivatives are disclosed in D16.
N-methylstylopium chloride (6) is disclosed in D18.

Re Item V.

i. Medical use of quaternary nitrogen containing derivatives of the alkaloids of original claim 4 excluding sanguinarine (cf. point VIII(i) below):

Novelty

There would appear to be only one anticipating document for the use of quaternary nitrogen derivatives used as medicines, this being in document D1 (Chinese) where N-methylprotopine chloride is tested on patients suffering from malaria. A disclaimer has been introduced into claims 12 and 21 for N-methylprotopine chloride. The subject-matter of claims 12-25* (* see Item III above) would therefore appear novel.

Inventive Step

Other than sanguinarine and N-methylprotopine chloride, no other alkaloids derivable from Chelidonium Majus L. have been tested for their possible pharmacological acitivity. An inventive step can be acknowledged for the subject-matter of claims 12-25 firstly because the skilled person has no incentive from D1 to further investigate the N-methylprotopines as they proved inactive in D1 against malaria and secondly because the skilled person has no indication that quaternerising the nitrogen in other alkaloids as in sanguinarine would provide compounds with pharmaceutical activity.

ii. The method of preparation of the alkaloid derivatives

With the alkaloid derivatives prepared by the method of amended claim 1 being known entities, the object of the present application would appear to lie in the provision of an alternative method for their preparation. The presently-claimed method is to be seen as new over the methods mentioned in the publications disclosing compounds falling under the scope of the compounds prepared according to amended claim 1. As the applicant has correctly pointed out, it is the washing step with water which is missing in the prior art.

The applicant has discovered that, by including this washing step with water after the alkylation step, the yield of the desired end product is unexpectedly increased compared to a washing step using organic solvents. Additionally, the water washing step removes any water-soluble components residing in the reaction mixture after the alkylating step. The increased yield obtained using this water washing step gives rise to the acknowledgement of an inventive step for the presently-claimed process.

Re Item VIII.

Concerning Sanguinarine, this is an alkaloid which already possesses a quaternary nitrogen atom with the nitrogen being bonded thought an imine link to a vicinal carbon atom. Sanguinarine would therefore not react with the alkylating agent. Sanguinarine and its salts are already known in the art to treat a number of ailments as is demonstrated in documents D2, D3, D6-D9, D17.

soluble in organic solvents, such as benzene, ether or chloroform, it is proposed in the prior art methods to remove the unreacted tris(1-aziridinyl)phosphine sulphide from the synthesis mixture by washing the reaction products with ether.

While the aforementioned prior art methods for the manufacture of pharmacologically active chelidonine derivatives have in common that they require purification of the final product using inflammable or even explosive organic solvents, it was now found that the purification could also and with even better results be accomplished using an aqueous solvent.

In Zhao Y et al., Chinese Pharmaceutical Bulletin (Yaoxue Tongbao) 16 (1981) 7 - 10 and Database Chemical Abstracts (Online), Database accession no. 1982:173909 a possible pharmacological effect of N-methylprotopine chloride on patients suffering from malaria is studied.

The alkaloid sanguinarine and its salts are known in the art to display a wide spectrum of biological activities.

Tanaka S et al., Planta Med 67 (2001) 108 - 113 describes an anti-inflammatory effect of sanguinarine chloride.

Schmeller T et al., Phytochemistry 44 (1997) 257 - 266 describes a biochemical activity of sanguinarine mediating chemical defense against microorganisms, viruses and herbivores in plants.

Walterova D et al., Journal of Medicinal Chemistry 24 (1981) 1100 - 1103 describes an inhibitory effect of sanguinarine on the enzymatic activity of liver alanine aminotransferase activity.

Ishii H et al., Chemical and Pharmaceutical Bulletin 33 (1985) 4139 - 4151 and Nakanishi T et al., Journal of Natural Products 62 (1999) 864 - 867 describe an antitumor activity of sanguinarine.

Lombardini JB et al., Biochemical Pharmacology 51 (1996) 151 - 157 describes an inhibitory effect of sanguinarine on the enzymatic activity of a mitochondrial kinase from the rat heart.

Ulrichova J et al., Toxicology Letters 125 (2001) 125 - 132 describes a cytotoxic effect of sanguinarine on hepatocytes in cell culture.

The preparation of several alkaloid derivatives, different from chelidonin derivatives, are also known in the art.

Valpuesta M et al., Tetrahedon 58 (2002) 5053 - 5059 discloses the synthesis of several alkaloid derivatives -*cis* and *trans* N-methyl-1-methoxystylopinium salts- from the alkaloid coulteropine, the main alkaloid from *Romneya coulteri,* in organic solvents.

Slavik J et al., Collection of Czechoslowak Chemical Commmunications 41 (1976) 285 - 289 discloses the isolation of alkaloid derivatives in the form of iodides and perchlorates from the roots of *Argemone platyceras* LINK et OTTO.

Schmidt E, Achiv der Pharmazie 231 (1893) 168 - 183 discloses the preparation of γ- homochelidonin-methyliodide by heating the pure base with an excess of methyliodide and recystallisation of the reaction product from alcohol.

Takao N et al., Chemical and Pharmaceutical Bulletin 21 (1973) 1096 - 1102 discloses the preparation of the 11-epicorynolin-iodine methylate by reaction of the alkaloid 11-epicorynolin from *Corydalis incisa* with methyliodide in a mixture of organic solvents and recystallisation of the reaction product from the mixture of organic solvents.

Danckwortt PW, Archiv der Pharmazie 250 (1912) 590 - 646 discloses the preparation of protopin-methyliodide by the reaction of protopin dissolved in acetone and an excess of methyliodide and recystallisation of the reaction product from alcohol.

Manske RHF et al., Journal of the American Chemical Society 64 (1942) 1659 - 1661 discloses the preparation of hunnemanine-O-ethyl ether methosulfate from the alkaloid hunnemanine isolated from *Hunnemannia fumariaefolia Sweet*.

Redemann CE et al., Journal of the American Chemical Society 71 (1949) 1030 - 1034 discloses the preparation of several allocryptopine derivatives, wherein the alkaloid allocryptopine was extracted from *Faraga coco* and the reactions were carried out in an organic solvent.

Zhang G-L et al., Phytochemistry 40 (1995) 299 - 305 discloses the extraction and structural analysis of the alkaloid N-methylstylopium chloride from the Chinese medical plant *Dactylicapnos torulosa*.

As for the chelidonin derivatives the aforementioned prior art preparations for different alkaloid derivatives do not include or suggest a washing step using an aqueous solvent.

CLAIMS

(Antrag vom 21.10.2004

1. A process for the manufacture of an alkaloid reaction product comprising at least one alkaloid derivative having a quaternary nitrogen, the process comprising:

a) providing a reaction mixture comprising an organic solvent, at least one alkaloid present in the herb *Chelidonium majus L.* and preferably selected from the group consisting of chelidonine, protopine, stylopine, allocryptopine, homochelidonine, chelamidine, chelamine, L-sparteine and oxychelidonine, and an alkylating agent, and carrying out an alkylation reaction by reacting the at least one alkaloid with the alkylating agent in the presence of the organic solvent, to allow for the formation of at least one alkaloid derivative having a quaternary nitrogen;

b) after termination of the reaction subjecting the resulting reaction mixture to at least one washing step with an aqueous solvent or water, to remove water-soluble compounds present in the reaction mixture; and

c) subjecting the washed reaction mixture to a treatment with a strong acid in gaseous or liquid form, preferably with gaseous hydrogen chloride or a hydrogen chloride solution, thereby converting at least one quaternary alkaloid derivative into a water soluble form, particularly a water-soluble salt.

2. The process of claim 1 wherein in step c) a reaction product precipitates during or after the treatment with acid, whereafter the precipitate is separated from the organic solvent, and optionally further purified using organic solvents.

3. The process of claims 1 or 2, wherein the alkylation reaction is carried out at elevated temperature, in particular at the boiling point of the solvent.

4. The process according to any one of claims 1 to 3, wherein a mixture of several or all alkaloids of *Chelidonium majus L.*, is used as an alkaloid source.

5. The process according to any one of claims 1 to 4, wherein chelidonine, oxychelidonine, or methoxychelidonine is applied as a sole alkaloid source.

6. The process according to any one of claims 1 to 5, wherein the alkylating agent is a physiologically active agent, preferably a cytotoxic agent.

7. The process according to any one of claims 1 to 6, wherein the alkylating agent is water-soluble or decomposes into water-soluble components upon contact with water.

8. The process according to any one of claims 1 to 7, wherein the organic solvent is selected from the group consisting of monochloromethane, dichloromethane, trichloromethane, monochloroethane, dichloroethane and trichloroethane.

9. The process according to any one of claims 1 to 8, wherein the alkylating agent is tris(1-aziridinyl)phosphine sulphide (CAS 52-24-4).

10. The process according to any one of claims 1 to 9, wherein said alkaloid derivative has a quaternary nitrogen atom to which, as a fourth ligand, a hydrogen residue or a residue originating from the alkylating agent is bound, the residue preferably being selected from the group consisting of a methyl, ethyl and a tris(1-aziridinyl)phosphine sulphide residue.

11. The process according to any one of claims 1 to 9, wherein said alkaloid derivative has a quaternary nitrogen atom and as a fourth ligand of said nitrogen a decomposition product formed due to the treatment with acid.

12. An alkaloid reaction product comprising at least one alkaloid derivative other than sanguinarine and M-methylprotopine chloride, the derivative having a quaternary nitrogen and the alkaloid being selected from the group of alkaloids present in the herb *Chelidonium majus L.* and preferably selected from the group consisting of chelidonine, protopine, stylopine,

allocryptopine, homochelidonine, chelamidine, chelamine, L-sparteine and oxychelidonine, for use as a drug or medicament.

13. The alkaloid reaction product according to claim 12, obtainable in a process according to any one of claims 1 to 11.

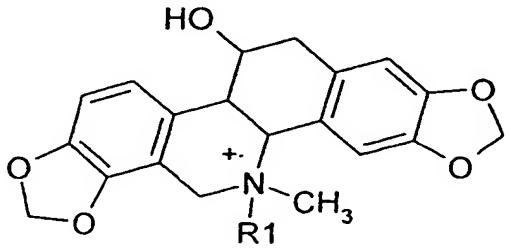
14. The alkaloid reaction product according to claim 13, obtained through reaction of one or more alkaloids with an alkylating agent, wherein in the derivative an initially tertiary nitrogen is present in quaternary form to which, as a fourth ligand, a hydrogen residue or a residue originating from the alkylating agent is bound, the residue preferably being selected from the group consisting of a methyl, ethyl, and tris(1-aziridinyl)phosphine sulphide residue, or from a part of tris(1-aziridinyl)phosphine sulphide.

15. The alkaloid reaction product according to claim 13 or 14, wherein at least one alkaloid derivative is present in the form of a water-soluble salt, preferably in the form of a hydrochloride.

16. The alkaloid reaction product according to any one of claims 13 to 15, wherein chelidonine, oxychelidonine, or methoxychelidonine is present as a sole alkaloid source.

17. The alkaloid reaction product according to any one of claims 13 to 16, wherein the product further comprises at least one compound selected from the group consisting of unreacted tertiary alkaloids, unreacted alkylating agent, and decomposition products of the alkylating agent.

18. A chelidonine derivative, wherein the naturally occurring chelidonine is present in a quaternated form according to the subsequent formula (I),



(I)

wherein as a fourth ligand R1 to the quaternary nitrogen a hydrogen or a methyl or ethyl residue is present, for use as a drug or medicament.

19. The chelidonine derivative of claim 18 in water soluble form, preferably as a salt with a strong acid, most preferably in the form of a hydrochloride.

20. The chelidonine derivative according to claim 18 or 19, which is characterized by the NMR spectrum in Fig.4, the UV spectrum in Fig.5, the mass spectrum in Figures 7 and 8, and the elementary analysis in Table 1.

21. Use of an alkaloid reaction product comprising at least one alkaloid derivative other than sanguinarine and M-methylprotopine chloride, the derivative having a quaternary nitrogen and the alkaloid being selected from the group of alkaloids present in the herb *Chelidonium majus L.* and preferably selected from the group consisting of chelidonine, protopine, stylopine, allocryptopine, homochelidonine, chelamidine, chelamine, L-sparteine and oxychelidonine, in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a disease or bodily condition selected from the group consisting of viral infection, cancer, immunological dysfunction, metabolic dysfunction and radiation damage.

22. Use according to claim 21, wherein the disease is selected from the group consisting of allergies, osteoporosis, skin tumours, influenza virus infections, rheumatic diseases, scars, postoperative wounds, epilepsy and multiple sclerosis.

23. Use according to claim 21 or 22, wherein the sole alkaloid is chelidonine and the alkaloid reaction product is characterized by the NMR spectrum in Fig.4, the UV spectrum in Fig.5, the mass spectrum in Figures 7 and 8, and the elementary analysis in Table 1.

24. Use of the chelidonine derivative claimed in claims 18 to 20 in the manufacture of a pharmaceutical composition for the prophylaxis or treatment of a disease or bodily condition selected from the group consisting of viral infection, cancer, immunological dysfunction, metabolic dysfunction and radiation damage.

25. Use according to claim 24, wherein the disease is selected from the group consisting of allergies, osteoporosis, skin tumours, influenza virus infections, rheumatic diseases, scars, postoperative wounds, epilepsy and multiple sclerosis.